DOI:10.1111/j.1365-2125.2007.02920.x

Anti-factor Xa activity of enoxaparin administered at prophylactic dosage to patients over 75 years old

A. Berges,[1] S. Laporte,[1] M. Epinat,[2] P. Zufferey,[3] E. Alamartine,[4] B. Tranchand,[5,6,7] H. Decousus[1,2] & P. Mismetti[1,2] for the PROPHRE.75 study group*

[1]*Clinical Pharmacology Department,* [2]*Internal Medicine Department,* [3]*Anaesthesiology Department and* [4]*Nephrology Unit, Thrombosis Research Group (EA3065), University Hospital of Saint-Etienne, Saint-Etienne,* [5]*Centre Leon Berard and* [6]*Lyon University, Lyon, and* [7]*EA3738, CTO, Faculty of Medicine Lyon Sud, Oullins, France*

What is already known about this subject

- Major bleeds with low-molecular-weight heparin have been reported at curative and prophylactic dosages.
- Enoxaparin clearance depends on body weight, and therefore weight-adjusted dosing is recommended to minimize interindividual variability in drug exposure and the risk of haemorrhage in patients treated at curative doses.
- Monitoring of this treatment is recommended in curative indications in patients at risk.
- The need for monitoring of patients at risk receiving prophylactic doses of enoxaparin, in this case the elderly, remains unclear.

What this study adds

- Clearance of enoxaparin at prophylactic doses is predictably related to body weight and creatinine clearance in the elderly.
- The simplified Modification of Diet in Renal Disease formula seems to be most discriminating and powerful in detecting any influence of glomerular filtration rate in the elderly.
- The influence of these covariates does not seem to be sufficiently clinically relevant to support routine assessment in the elderly.

Correspondence
Silvy Laporte, EA3065 (Thrombosis Research Group), Clinical Pharmacology Department, University Hospital of Saint-Etienne, Bellevue Hospital, 42055 Saint-Etienne, France.
Tel: + 33 4 7712 0572
Fax: + 33 4 7712 7820
E-mail: silvy.laporte@chu-st-etienne.fr

*See Appendix 1.

Keywords
drug monitoring, elderly, enoxaparin, low-molecular-weight heparin, NONMEM, pharmacokinetic

Received
13 July 2006
Accepted
27 February 2007
Published *OnlineEarly*
17 May 2007

Aims
Major bleeding complications with low-molecular-weight heparin (LMWH) treatment have been reported both in clinical studies and during postmarketing surveillance. Monitoring of antifactor Xa (anti-Xa) activities is therefore recommended in special populations often predisposed to renal impairment. The PROPHRE.75 study was conducted to estimate the distribution parameters of anti-Xa activity in the elderly.

Methods
PROPHRE.75 was a prospective study of a cohort of consecutive patients aged >75 years and treated with 4000 IU of enoxaparin once daily for venous thromboembolism prophylaxis. Dosing history and measurements of anti-Xa activity in sparse samples were recorded throughout treatment. The covariates included weight, gender, age, renal function, medical history and concomitant medication. Population parameters and interindividual variability were estimated using NONMEM® V software.

Results
Anti-Xa activity was studied in 189 patients (mean age 82 ± 5 years, 22% weighing <50 kg, 50% presenting renal impairment according to the Cockcroft and Gault formula). A first-order input two-compartment model best fitted the data. Clearance was significantly related to body weight and creatinine clearance based on the simplified Modification of Diet in Renal Disease formula, central volume being related to body weight. According to individual Bayesian estimations, 4% of patients presented with a peak anti-Xa activity >1.0 IU ml^{-1}, but this group did not include the sole patient experiencing a major bleed (0.53%).

Conclusions
Systematic monitoring of anti-Xa activity in elderly patients treated with enoxaparin at prophylactic doses does not seem to be necessary to prevent the occurrence of major bleeding.

Introduction

Due to their efficacy, safety and convenience, low-molecular-weight heparins (LMWH) are becoming the standard treatment for the prevention and treatment of venous and arterial thrombotic diseases [1–5]. The expanding use of LMWH has given rise to reports of major bleeding complications, especially in elderly patients, in the context of both randomized and observational clinical studies and postmarketing surveillance.

As LMWH are excreted mainly via the kidneys [6], repeated administration of therapeutic doses to patients with renal failure may lead to accumulation, overdose and risk of bleeding events. Monitoring of antifactor Xa (anti-Xa) activity is therefore recommended by the French authorities in curative indications and in special situations such as treatment of the elderly, who are often predisposed to renal impairment [7, 8].

These recommendations raise the issues of how to monitor accurately the anti-Xa activity of LMWH and what target range should be used. Several randomized studies have been performed to assess the value of monitoring anti-Xa activity, but these have shown no difference in terms of efficacy and/or safety between patients treated by LMWH and monitored according to a prespecified target range of anti-Xa values and patients in whom anti-Xa activity was not monitored [9–11]. The absence of any difference could be due either to the inclusion of 'too normal' patients who did not require monitoring in view of their low biological variability, or to the use of an inappropriate prespecified target range in the trial, or to the fact that such monitoring is not useful. Monitoring could be valuable if a high variability in anti-Xa activity is expected in specific populations. This question is particularly relevant with regard to the elderly, because LMWH are widely and routinely prescribed for geriatric populations, predisposed to both thrombotic diseases and bleeding [12]. Finally, as LMWH are not interchangeable [13], due to their different dosage regimens, the range of anti-Xa activities expected in everyday practice should be determined for each LMWH.

We therefore conducted a population pharmacokinetic study of enoxaparin administered at prophylactic doses in everyday practice to estimate anti-Xa activity and its variability in the elderly, and to identify the factors potentially leading to interindividual variability.

Methods

Study design

PROPHRE.75 was a prospective study of a cohort of elderly patients treated with prophylactic doses of enoxaparin in medical and surgical departments (Internal Medicine Department, Geriatric Department, Orthopaedic Surgery Unit).

Patients and treatments

All patients >75 years old and requiring enoxaparin for venous thromboembolism prophylaxis in a medical or surgical context were eligible for the study. All patients gave their oral consent to participation in the trial. The database was approved by the French consultative committee 'Commission Nationale de l'Informatique et des Libertés'. Exclusion criteria comprised any contraindication to the use of prophylactic doses of LMWH and indication for curative anticoagulant treatment. Each patient included was treated with the recommended enoxaparin regimen comprising subcutaneous injection of 4000 IU once daily.

Data

Blood samples were collected routinely throughout treatment. As heparin concentration cannot be measured, anti-Xa activity is commonly considered to be an acceptable surrogate for enoxaparin concentration [14]. Venous blood was collected in sodium-citrated tubes. Anti-Xa activity was measured by a validated chromogenic assay (Biophen® heparin [6]; HYPHEN BioMed, Neuville-sur-Oise, France) with a lower limit of detection of 0.05 IU ml^{-1}. The quality of anti-Xa activity determination was assessed using control human plasmas for the quality control of LMWH tests containing different levels of anti-Xa activity: approximately 0.80 and 1.20 IU ml^{-1} (Biophen® LMWH Control Plasma) and approximately 0.25 and 0.50 IU ml^{-1} in the low concentration range (Biophen® LMWH Control Low). The interassay precision (coefficient of variation) determined using the control human plasmas was <2.5%. Variables recorded in routine geriatric practice were: demographic data (age, weight, gender), medical history (diabetes, cancer, hypertension, etc.) and concomitant medication (nonsteroidal anti-inflammatory drugs, antiplatelet agents, etc.). Renal function was estimated by measuring serum creatinine (Scr) using an enzymatic method, calculating creatinine clearance (CrCl) according to the Cockcroft and Gault formula [15], and the simplified Modification of Diet in Renal Disease (MDRD) formula [16, 17].

Population pharmacokinetic analysis

Several base compartmental models previously used to fit enoxaparin anti-Xa activities were tested in the population pharmacokinetic analysis. The models depicted were based on one or two compartments, with various

expressions for absorption and/or elimination, and with or without the inclusion of endogenous activity [18–24]. Data below the limit of quantification (LOQ) were excluded (0.05 IU ml^{-1}). The use of other methods to analyse these data (replacement of data below LOQ by LOQ/2 or replacement of the first value below LOQ determined for each patient by LOQ/2 and omission of all following values below LOQ) [25] did not change the fit of the model (data not shown). Various error models (additive, multiplicative and combined) were investigated. Interindividual variabilities in parameters were implemented as exponential terms, for example, with regard to clearance (CL):

$$CLj = CLp \times \exp(\eta_{jCL})$$

where η_{jCL} denotes the proportional difference between the true individual parameter (CLj) and the mean population value (CLp).

Model building

Pharmacokinetic analyses were carried out using NONMEM software (Version 5.1; Globomax Service Group, Hanover MD, USA) [26, 27]. NONMEM, standing for NON-linear Mixed Effects Models, allows estimation of the following pharmacokinetic parameters: Θ, interindividual variability, ω, of each parameter and residual variability σ. The First Order Condition with interaction (FOCE inter) estimation method was used. Individual pharmacokinetic parameters were obtained using empirical Bayesian estimations.

The following procedure was used to identify the influence of the covariates on interindividual variability in the parameters [28]. In the first step, the base population model, without any covariates, was constructed. In the second step, relationships between individual parameters and potential covariates were investigated, using linear regression for continuous covariates (age, weight, Scr, CrCl, etc.), tree-based modelling and a generalized additive model (GAM) procedure implemented in Splus. In the third step, candidate parameter covariates were added to the model if they improved the fit, as judged by a decrease in the objective function of >3.84 in the likelihood ratio test (χ^2, $P < 0.05$; one degree of freedom). A procedure of backward elimination of each significant covariate was then performed. A covariate was excluded if the minimum objective function did not increase by >6.6 (χ^2, $P < 0.01$; one degree of freedom).

Model validation procedure

If the model is to be used for predicting anti-Xa values, it should at least be capable of regenerating the data used for its construction. A predictive check might then offer insights into potential inconsistencies [29]. In this way, we assessed the quality of the model by simulating 200 datasets from the final parameter estimates and compared the observed distribution with the simulated distribution. A plot of the time course of the observations and prediction interval for the simulated values provided a visual predictive check, which confirmed the suitability of the final model [30].

Results

Patient data

A total of 189 patients entered the PROPHRE.75 study. Their characteristics are shown in Table 1. The mean age of the population was 82 ± 5 years (± SD), 50% of the patients being >81 years old. Most of the patients were women. Eight percent were considered as obese (body mass index ≥ 30 kg m^{-2}). Half of the patients presented moderate or severe renal failure (CrCl <50 ml min^{-1}) according to the Cockcroft and Gault formula, but <20% according to the simplified MDRD formula. The majority of the patients had been admitted for an acute medical condition (63%), the others were orthopaedic patients (15%) or had suffered a stroke (22%). Most patients were being treated with drugs affecting haemostasis (principally antiplatelet agents for atrial fibrillation). One major bleed (0.53%), defined as an intracranial haemorrhage, occurred during the study, requiring the interruption of enoxaparin treatment. Three symptomatic thrombotic events were observed (1.59%), necessitating curative treatment.

Sampling data

The mean duration of treatment was 7 days. A total of 451 serum anti-Xa activities were obtained, signifying on average fewer than three measurements per patient (very sparse data). Fifty-six activities below the limit of quantification were excluded. The distribution of sampling times covered the entire day. The most frequent sampling time was time 0, corresponding to the residual activity just before the morning injection, this time being most convenient for the nurses.

Model building

A two-compartment first-order input model with log normal interindividual variability in clearance (CL), volume of distribution of the central compartment (V_2), intercompartmental clearance (Q) and peripheral volume (V_3), including a proportional residual variance, was found to be the most suitable base structural model. Additional incorporation of an estimated endogenous activity over-parameterized the model without any improvement. A block matrix was added to take into

Table 1
Baseline characteristics of patients

Demographic and clinical data	$n = 189$
Age mean ± SD (min–max)	82 ± 5 years (75–95)
median	81 years
Women	62%
Weight mean ± SD (min–max)	66 ± 14 kg (38–108)
<55 kg	22%
Obese (BMI > 30 kg m^{-2})	8%
LMWH indications	
Immobility due to acute medical disease	63%
Orthopaedic surgery	15%
Stroke	22%
Renal function	
Scr	
Mean ± SD (min–max)	52 ± 17 ml min^{-1} (24–93)
Scr < 60 µmol l^{-1}	50%
CrCl, Cockcroft–Gault formula	
Mean ± SD (min–max)	52 ± 17 ml min^{-1} (24–93)
CrCl < 50 ml min^{-1}	50%
CrCl, simplified MDRD formula	
Mean ± SD (min–max)	69 ± 20 ml min^{-1} (27–127)
CrCl < 50 ml min^{-1}	18%
Bleeding risk factor	
Hypertension	57%
Diabetes	24%
Cancer	19%
Concomitant medication*	
Antiplatelet agents	36%
Corticosteroids	7%
NSAIDs	5%
Therapeutic doses of anticoagulant	2%

*Scr, Serum creatinine; NSAID, nonsteroidal anti-inflammatory drug; BMI, body mass index; LMWH, low-molecular-weight heparin. *Some patients might have received combination therapy.*

account the correlation between CL and V_2. The chronology of the modelling procedure presented in Table 2 illustrates the progression of the covariate modelling process based on the likelihood ratio test. An improvement in fit was found when body weight, CrCl based on the simplified MDRD formula and gender were incorporated as covariates for clearance (CL) and body weight in the volume of distribution of the central compartment (V_2). No other covariate seemed to influence the anti-Xa activity parameters. The full model was not improved by fitting a mixed residual error model. When the full model was tested against reduced models by omitting each covariate in turn, all covariates except gender remained significant. Standard diagnostic plots for the base and the covariate models are presented in Figure 1. Weighted residual plots revealed no apparent bias in the final model. Interindividual variabilities in CL and V_2, expressed as coefficients of variation, were reduced from 30% to 26% and from 28% to 15%, respectively, when considering weight and CrCl as covariates. The final estimated parameters are presented in Table 3.

Model evaluation procedure

A visual predictive check was performed on the base and covariate models to confirm improvement of the model and suitability of the final model (Figure 2). The base structural model without any covariates underestimated high anti-Xa activities; in contrast, a visual predictive check showed that addition of body weight and CrCl led to a much better description of the variability in high anti-Xa activity compared with the base model, but still did not properly capture the profile of anti-Xa activity at the beginning of the treatment (<48 h).

Bayesian predictions

Four patients were randomly chosen to illustrate the individual predictions of the model (Figure 3). Irrespective of the day of sampling, gender, age, CrCl and body weight, the model seemed to predict anti-Xa activities adequately. The distribution of individual Bayesian anti-Xa activities between 3 and 5 h after subcutaneous injection of enoxaparin (peak anti-Xa activities) ranged from 0.10 IU ml^{-1} to 1.20 IU ml^{-1} with a median of 0.44 IU ml^{-1}. Twenty-nine percent of patients had at least one estimated peak anti-Xa activity >0.5 IU ml^{-1}, 10% >0.8 IU ml^{-1} and 4% >1.0 IU ml^{-1}. These last patients ($n = 7$) had a low body weight (mean of 50 kg) and a low CrCl estimated using the simplified MDRD formula (mean of 74 ml min^{-1}); five of them were women. Finally, the patient who experienced a major haemorrhage showed an estimated peak anti-Xa activity of 0.35 IU ml^{-1} 4 h after LMWH injection.

Discussion

The PROPHRE.75 study presents the first population pharmacokinetic model of enoxaparin administered at prophylactic doses to patients aged >75 years. In view of the wide range of patients receiving this type of treatment (medical patients, those receiving prophylactic treatment in the context of orthopaedic and general surgery, etc.), it was interesting to investigate the

Table 2
Model-building steps

Description	Interindividual variability (CV)	Residual variability (CV)	Objective function (Δobj)*	*P*-value†	Covariate retained
Base model	CL 30% V_2 28% V_3 97%	31%	−1353		
Forward selection					
1. Weight on CL $CL = \theta 1 \times [wt/median(wt)]^{\theta 6}$	CL 26% V_2 25% V_3 90%	31%	−1366 (−13)	<0.001	Yes
2a. Serum creatinine on CL			−1366 (0)	NS	No
2b. Creatinine clearance (C–G) on CL $CL = \theta 1 \times [wt/median\ (wt)]^{\theta 6} \times [CrCl/median\ (CrCl)]^{\theta 7}$	CL 26% V_2 27% V_3 83%	30%	−1372 (−6)	<0.02	Yes
2c. Creatinine clearance (MDRD) on CL $CL = \theta 1 \times [wt/median\ (wt)]^{\theta 6} \times [CrCl/median\ (CrCl)]^{\theta 7}$	CL 28% V_2 26% V_3 84%	30%	−1375 (−9)	<0.01	Yes instead of the previous one
3. Gender on CL $CL = \theta 1 \times [wt/median\ (wt)]^{\theta 6} \times [CrCl/median\ (CrCl)]^{\theta 7}$ (x θ9 if male)	CL 27% V_2 27% V_3 89%	29%	−1382 (−7)	<0.01	Yes
4. Weight on V_2 $V_2 = \theta 2 \times [wt/median\ (wt)]^{\theta 8}$	CL 22% V_2 13% V_3 90%	29%	−1408 (−26)	0.0001	Yes
Backward selection					
Weight on CL omitted	CL 28% V_2 18% V_3 87%	30%	−1377 (−31)	<0.0001	Yes
Creatinine clearance (MDRD) on CL omitted	CL 24% V_2 18% V3 93%	31%	−1399 (−9)	<0.01	Yes
Gender on CL omitted	CL 26% V_2 15% V_3 93%	30%	−1402 (−6)	<0.02	No
Weight on V_2 omitted	CL 27% V_2 27% V_3 89%	30%	−1382 (−26)	<0.0001	Yes

*CL, Clearance; V, volume of distribution; WT, body weight; Scr, serum creatinine; C–G, Cockcroft–Gault formula; MDRD, simplified MDRD formula. *Δobj, Delta objective function compared with previous significant model. †Likelihood ratio test at the 0.05 significance level was used to discriminate between nested structural models that correspond to a reduction of 3.84 units (χ^2, $P < 0.05$) in the objective function (obj) with one parameter difference between models (forward selection). Covariates were not deleted from the model at a 0.01 level of significance (backward selection).*

potential covariates that could explain part of the interindividual variability of enoxaparin pharmacokinetic parameters, as well as the risk of drug accumulation. This population study has shown that body weight and CrCl, estimated using the simplified MDRD formula, significantly influence enoxaparin pharmacokinetics.

Despite the absence of any consensual pharmacokinetic model to describe enoxaparin's profile (Table 4), probably because model identification is design dependent (sparse or rich data) and population dependent, the covariates partly explaining interindividual variability are quite similar [18–24]. In fact, the main difference between studies concerns the methods used to summarize the covariates of interest (different size descriptors for weight and different renal function estimates). In our study performed in the elderly, it is important to note that CrCl based on the Cockcroft and Gault formula was not the best marker of renal function with regard to

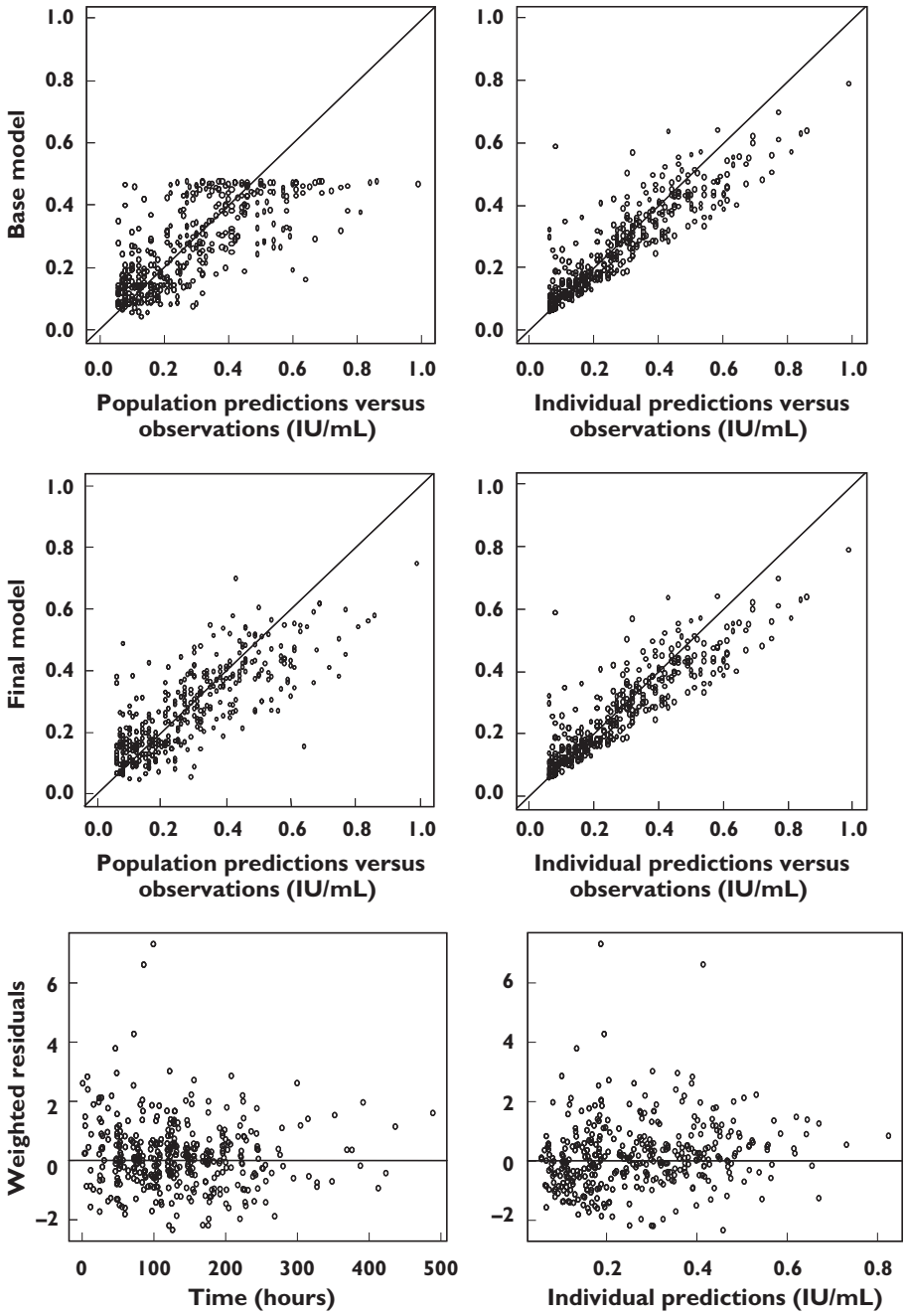

Figure 1
Standard diagnostic plots using base and covariate models

explaining part of the interindividual variability of enoxaparin CL. Some authors have noted that assessment of renal function based on Scr and CrCl estimated using the Cockcroft and Gault formula might be inaccurate in the elderly [31, 32]. The use of Levey's formula, better adapted to a geriatric population, permits more precise evaluation of renal function, but albumin and urea assessments are not easily available in current clinical practice [16, 32]. The simplified Levey formula, also called the simplified MDRD formula [17], also seems to be accurate in the elderly, with a discriminative power between several levels of CrCl in our study. Body weight is not taken into account in computing this formula, which avoids both the introduction of correlated variables in the pharmacokinetic model and a too frequent use of approximate body weight rather than an actual measurement, especially for very old patients who are not always sufficiently mobile to be simply weighed on a bathroom scale.

The pharmacokinetic analysis of the PROPHRE.75 trial allowed identification of two significant covariates in patients >75 years old: body weight and renal

Table 3
Final parameter estimates

Parameters	Values (95% CI)	Interindividual variability CV (95% CI)
KA (h^{-1})	0.63 (0.44, 0.81)	0 FIXED
CL ($l\,h^{-1}$) = $\theta1 \times (wt/65)^{\theta6} \times (ClCr/69)^{\theta7}$		26% (20, 31)
$\theta1$	0.70 (0.66, 0.75)	
$\theta6$	0.78 (0.47, 1.08)	
$\theta7$	0.25 (0.05, 0.45)	
V_2 (l) = $\theta2 \times (wt/65)^{\theta8}$		15% (0, 23)
$\theta2$	6.43 (5.47, 7.39)	
$\theta8$	1.25 (0.72, 1.78)	
Q ($l\,h^{-1}$)	0.34 (0.17, 0.49)	0 FIXED
V_3 (l)	8.18 (1.97, 14.36)	93% (22, 130)
Residual variability σ (CV)	30% (26, 33)	

The 95% confidence interval (CI) of point estimates was determined from the corresponding standard errors of estimates (SE), as follows: CI = point estimate ± 1.96 × SE. SE was calculated as the square root of the diagonal elements of the estimation covariance matrix.

function. The first comment is that the relationships between the pharmacokinetic parameters of LMWH and body weight were already known with respect to curative doses (Table 4); the second is that these relationships are in agreement with well-established allometric equations, corresponding to estimates of 0.78 in the equation relating CL to body weight and 1.25 in that relating V_2 to body weight in our study and 0.75 and 1, respectively, in allometric equations [33, 34].

This result is in accordance with previously published data on LMWH treatment at curative doses in relation to kidney function [19, 21–23, 35, 36]. However, a statistically significant correlation does not necessarily signify a clinically relevant effect. What of the clinical impact of renal function in this pharmacokinetic study?

First, if we look at the concentration–time profiles and Bayesian maximal anti-Xa activities obtained for individual patients, 4% of patients presented a peak anti-Xa activity, reaching at least the empirical threshold for bleeding risk (i.e. 1.0 IU ml^{-1}, empirical because defined without any clinical evaluation) [37]. The low percentage of these patients, combined with the absence of a clear relationship with bleeding risk, does not support systematic laboratory monitoring in the elderly.

Second, while enoxaparin CL is lower in patients with impaired renal function and low body weight, the variation is slight, even though statistically significant. Indeed, the results of a simulation indicated that the increase in the terminal elimination half-life of enoxaparin between a woman weighing 45 kg with a CrCl of 25 ml min^{-1}, according to the simplified MDRD formula, and a man weighing 75 kg with normal renal function (69 ml min^{-1}) is <1.5 h. This increase is of questionable clinical relevance and cannot of itself imply an increased risk of drug accumulation. The same clinical conclusions were drawn in a very recent paper investigating the mean peak and trough values of anti-Xa activity observed after administration of prophylactic (i.e. low) doses of enoxaparin in the elderly [38].

Finally, some clinicians choose to monitor anti-Xa activity in the elderly systematically in order to reduce the dose when the peak anti-Xa activity reaches the cut-off value of 1.0 IU ml^{-1} [37]. Several studies have been conducted to establish relationships between anti-Xa activities and LMWH efficacy and safety, the main issue being the balance between antithrombotic and haemorrhagic risks. Clinicians who prescribe reduced doses of enoxaparin for fear of bleeding complications should be aware of the risks. This practice can lead to decreased anti-Xa activity and, consequently, insufficient reduction in the risk of thromboembolic events. Indeed, the MEDENOX study has shown that the use of an enoxaparin dose of 2000 IU instead of 4000 IU results in an efficacy equivalent to that of a placebo with regard to the prevention of venous and arterial thrombotic diseases [3]. Similarly, Montalescot *et al.* have demonstrated that a low dose of enoxaparin is an independent predictor of 30-day mortality in unselected patients with acute coronary syndrome [39].

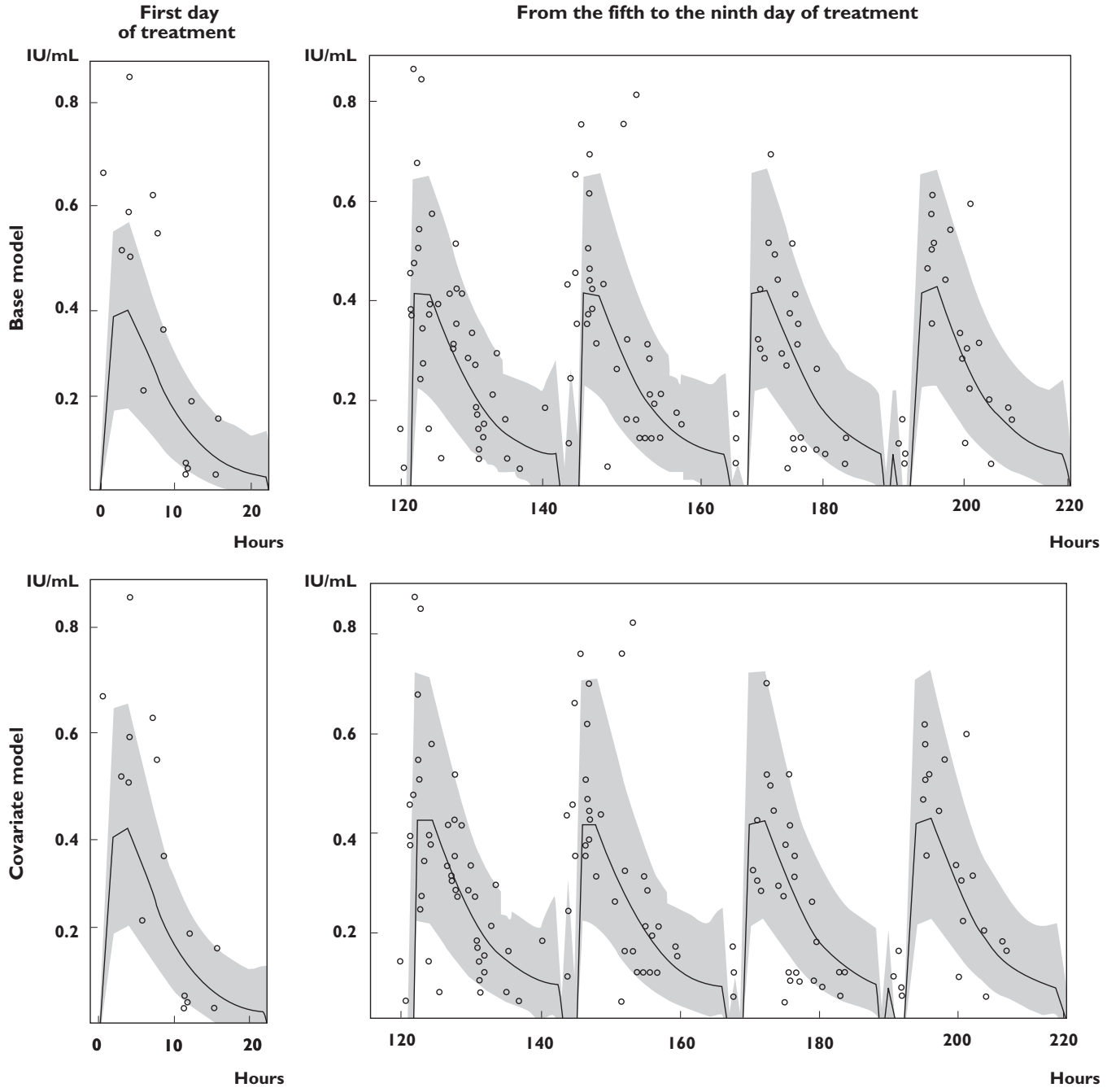

Figure 2

Visual predictive checks of base and covariate models (constructed from 200 posterior predictive plots). 95% posterior predictive interval; observations (IU/mL) (○); median (—)

Our cohort is clearly not sufficiently large to show any correlation between anti-Xa activity after prophylactic doses of enoxaparin and bleeding risk, as only one event (0.53%) was observed. Systematic assessment of anti-Xa activities and consequently reduction of enoxaparin doses in the prophylactic context cannot be routinely recommended for the time being, assuming that the conditions of administration are respected. Nevertheless, little information concerning prophylactic treatment with enoxaparin has been published and further investigations in this area are required.

Competing interests: None declared.

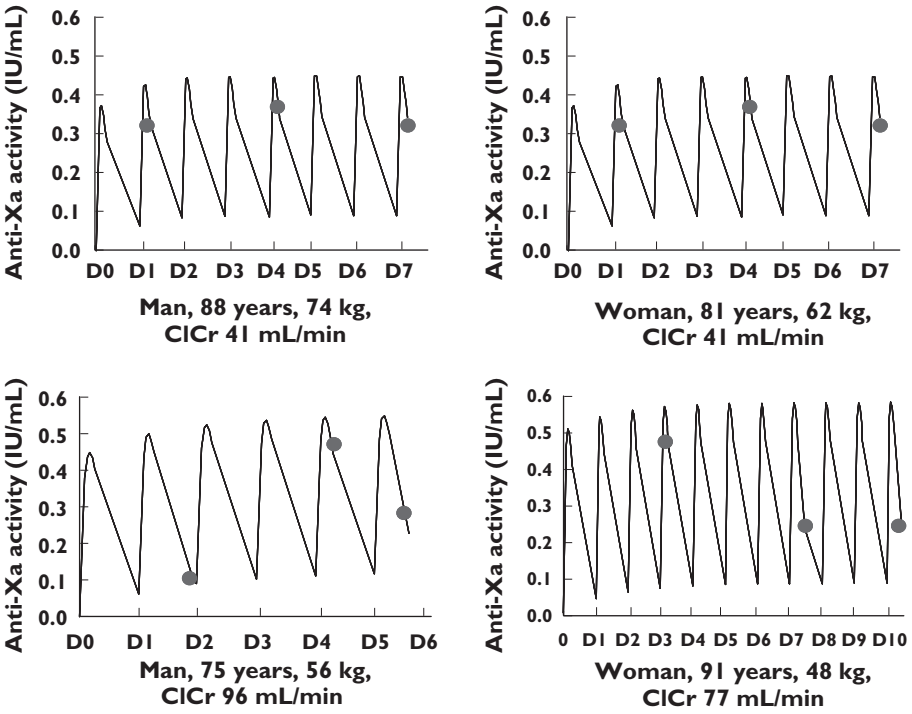

Figure 3
Individual prediction using the covariate model. Observations (IU/mL) (●), individual predictions (—); D = days, ClCr estimated by the simplified MDRD formula

Table 4
Enoxaparin pharmacokinetic models

	Schoemaker 1996 [18]		Bruno 2003 [19]	Green 2003 [20]	Green 2005 [21]	Hulot 2004 [22]	Hulot 2005 [23]	Kane-Gill 2005 [24]	Present study
Indication	–		ACS	ACS, DVT	ACS	ACS	ACS	CII	Med, surg,
	curative		curative	curative	curative	curative	curative	curative	prophylactic
Daily dosage	Not available		250 IU kg^{-1} then 4000 IU	200 IU kg^{-1}	100–200 IU kg^{-1}	200 IU kg^{-1}	200 IU kg^{-1}	550 IU h^{-1} (initial)	4000 IU
Number of patients	12		448	96	38	60	532	48	189
Median age, years	Not available		63	56 (mean)	78	74 (mean)	67 (mean)	59 (mean)	81
Total anti-Xa activities	120		788	NA	313	189	661	363	451
(number per patient)	(10)		(1.8)	(3)	(8.2)	(3)	(1.2)	(8)	(2.4)
PK model: number of compartments	1	2	1	2	2	1	1	1	2
Endogenous anti-Xa activity	Yes	No	No	No	Yes	No	No	No	No
Significant covariates									
On clearance	_		BW, CrCl (Cockcroft–Gault with BW)	Lean body weight	CrCl (Cockcroft–Gault with IBW)	Scr, gender	BW, Scr, gender	BW	BW, CrCl (simplified MDRD with BW)
On volume of distribution	_		_	BW	BW	BW	BW	ICU	BW

NA, Not available; ACS, acute coronary syndrome; DVT, deep-vein thrombosis; CII, continuous intravenous infusions; med, medical patients; surg, surgical patients; BW, body weight; IBW, ideal body weight; Scr, serum creatinine; CrCl, creatinine clearance; ICU, intensive care unit; PK, pharmacokinetic.

The PROPHRE.75 study, conducted in the University Hospital of St Etienne, was supported by a grant from PHRC 2001 (Ministère de la Santé). The authors are indebted to P. Girard and C. Dartois for their helpful scientific advice and to the chairmen of the Model Building Session at the PAGE 2005 meeting (M. Karlsson, Ph. Jacqmin, S. Duffull). They sincerely thank the anonymous reviewers who have greatly contributed to improvement of the paper.

Appendix 1: PROPHRE.75 Study Group

All members of the group work in the University Hospital of Saint-Etienne, France.

Investigators: Internal Medicine Department, Bellevue Hospital (D. Delsart, M. Epinat, V. Bost): 151 patients. Anaesthesiology Department, Bellevue Hospital (P. Zufferey, S. Passot, P. Bouffard): 53 patients. Geriatric Medicine Department, Bellevue Hospital (C. Ferron): seven patients. Geriatric Department, La Charité Hospital (R. Gonthier): five patients.

Assay: Department of Haemostasis (B. Tardy, J. Reynaud).

Coordinating centre: Thrombosis Research Group (EA3065), Clinical Pharmacology Department (P. Mismetti, S. Laporte, V. Bost, C. Bernabé) and Nephrology Unit (E. Alamartine).

Data Management: Thrombosis Research Group (EA3065), Clinical Pharmacology Department (S. Laporte, A. Berges, C. Labruyere, E. Presles).

References

1 Zufferey P, Laporte S, Quenet S, Molliex S, Auboyer C, Decousus H, Mismetti P. Optimal low-molecular-weight heparin regimen in major orthopaedic surgery. A meta-analysis of randomised trials. Thromb Haemost 2003; 90: 654–61.

2 Mismetti P, Laporte S, Darmon JY, Buchmüller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. Br J Surg 2001; 88: 913–30.

3 Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Nguyen H, Olsson CG, Turpie AG, Weisslinger N. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients (MEDENOX). N Engl J Med 1999; 341: 793–800.

4 Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med 2000; 160: 181–8.

5 Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. Lancet 2000; 355: 1936–42.

6 Boneu B, Cadroy Y, Dol F, Caranobe C, Sie P. Pharmacocinétique des héparines. Angeiologie 1986; 38: 133–45.

7 Campbell NR, Hull RD, Brant R, Hogan DB, Pineo GF. Aging and heparin related bleeding. Arch Intern Med 1996; 156: 857–60.

8 AFSSaPS. Information des prescripteurs sur l'utilisation des HBPM. J Mal Vasc 2002; 27: 231–3. (http://www.AFSSaPS.sante.fr).

9 Nieuwenhuis HK, Albada J, Banga JD, Sixma JJ. Identification of risk factors for bleeding during treatment of acute venous thromboembolism with heparin or low molecular weight heparin. Blood 1991; 78: 2337–43.

10 Levine MN, Planes A, Hirsh J, Goodyear M, Vochelle N, Gent M. The relationship between anti-factor Xa activity and clinical outcome in patients receiving enoxaparin low molecular weight heparin to prevent deep vein thrombosis after hip replacement. Thromb Hemost 1989; 62: 940–4.

11 Boneu B, de Moerloose P. How and when to monitor a patient treated with low molecular weight heparin. Semin Thromb Hemost 2001; 27: 519–22.

12 Anderson FA, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovie B, Forcier A, Dalen JE. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. Arch Intern Med 1991; 151: 933–8.

13 White RH, Ginsberg JS. Low-molecular-weight heparins: are they all the same? Br J Haematol 2003; 121: 12–20.

14 Bara L, Planes A, Samama MM. Occurrence of thrombosis and haemorrhage, relationship with anti-Xa, anti-IIa activities, and D-dimer plasma levels in patients receiving a low molecular weight heparin, enoxaparin or tinzaparin, to prevent deep vein thrombosis after hip surgery. Br J Haematol 1999; 104: 230–40.

15 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31–41.

16 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999; 130: 461–70.

17 Levey AS, Greene T, Kusek JW, Beck GL, MDRD Study Group. A simplified equation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol 2000; 11: 155A.

18 Schoemaker RC, Cohen AF. Estimating impossible curves using NONMEM. Br J Clin Pharmacol 1996; 42: 283–90.

19 Bruno R, Baille P, Retout S, Vivier N, Veyrat-Follet C, Sanderink GJ, Becker R, Antman EM. Population pharmacokinetics and pharmacodynamics of enoxaparin in unstable angina and non-ST-segment elevation myocardial infarction. Br J Clin Pharmacol 2003; 56: 407–14.

20 Green B, Duffull SB. Development of a dosing strategy for enoxaparin in obese patients. Clin Pharmacol 2003; 56: 96–103.

21 Green B, Greenwood M, Saltissi D, Westhuyzen J, Kluver L, Rowell J, Atherton J. Dosing strategy for enoxaparin in patients with renal impairment presenting with acute coronary syndromes. Br J Clin Pharmacol 2005; 59: 281–90.

22 Hulot JS, Vantelon C, Urien S, Bouzamondo A, Mahé I, Ankri A, Montalescot G, Lechat P. Effect of renal function on the pharmacokinetics of enoxaparin and consequences on dose adjustment. Ther Drug Monit 2004; 26: 305–10.

23 Hulot JS, Montalescot G, Lechat P, Collet JP, Ankri A, Urien S. Dosing strategy in patients with renal failure receiving enoxaparin for the treatment of non-ST-segment elevation acute coronary syndrome. Clin Pharmacol Ther 2005; 77: 542–52.

24 Kane-Gill SL, Feng Y, Bobek MB, Bies RR, Pruchnicki MC, Dasta JF. Administration of enoxaparin by continuous infusion in a naturalistic setting: analysis of renal function and safety. J Clin Pharm Ther 2005; 30: 207–13.

25 Duval V, Karlsson M. Impact of omission or replacement of data below the limit of quantification on parameter estimates in a two-compartment model. Pharmaceut Res 2002; 19: 1835–40.

26 Beal SL, Sheiner LB. NONMEM Users Guides. San Francisco: NONMEM Project Group, University of California at San Francisco 1992.

27 Beal SL, Sheiner LB. Estimating population kinetics. Crit Rev Biomed Eng 1982; 8: 195–222.

28 Mandema JW, Verotta D, Sheiner LB. Building population pharmacokinetic–pharmacodynamic models. I. Models for covariate effects. J Pharmacokinet Biopharm 1992; 20: 511–28.

29 Pravin RJ, Jogarao Gobburu VS. A new equivalence based metric for predictive check to qualify mixed-effects models. AAPS J 2005; 7: E523–31.

30 Holford N. The visual predictive check—superiority to standard diagnostic (Rorschach) plots. PAGE 2005; 14: 738 (Abstr.).

31 Tett SE, Kirkpatrick CM, Gross AS, McLachlan AJ. Principles and clinical application of assessing alterations in renal elimination pathways. Clin Pharmacokinet 2003; 42: 1193–211.

32 Fehrman-Ekholm I, Skeppholm L. Renal function in the elderly (>70 years old) measured by means of Iohexol clearance, serum creatinine, serum urea and estimated clearannce. Scand J Urol Nephrol 2004; 38: 73–7.

33 Knibbe CAJ, Zuideveld KP, Aarts LPHJ, Kubs FM, Danhof M. Allometric relationships between the pharmacokinetics of propofol in rats, children and adults. Br J Clin Pharmacol 2005; 59: 705–11.

34 Holford NHG. A size standard for pharmacokinetics. Clin Pharmacokinet 1996; 30: 329–32.

35 Mismetti P, Laporte-Simitsidis Navarro C, Sié P, d'Azemar P, Necciari J, Duret JP, Gaud C, Decousus H, Boneu B. Aging and venous thromboembolism influence the pharmacodynamics of the anti-factor Xa and anti-thrombin activities of a low molecular weight heparin (nadroparin). Thromb Haemost 1998; 79: 1162–5.

36 Collet JP, Montalescot G, Choussat R, Lison L, Ankri A. Enoxaparin in unstable angina patients with renal failure. Int J Cardiol 2001; 80: 81–2.

37 Hirsh J, Raschke R. Heparin and low-molecular-weight heparin. 7th ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004; 3 (Suppl.): 188S–203S.

38 Mahe I, Gouin-Thibault I, Simoneau G, Drouet L, Di Castillo H, Siguret V, Bergmann JF, Pautas E. Medical elderly patients treated with prophylactic doses of enoxaparin: influence of renal function on anti-Xa activity level. Drug Aging 2007; 25: 63–71.

39 Montalescot G, Collet JP, Tanguy ML, Ankri A, Payot L, Dumaine R, Choussat R, Beygui F, Gallois V, Thomas D. Anti-Xa activity relates to survival and efficacy in unselected acute coronary syndrome patients treated with enoxaparin. Circulation 2004; 110: 392–8.